B. Summary Chart of Prior Clinical Studies

List and comments on clinical trials leading up to the Swedish RCT

1. Reference: Arulkumaran S, Lilja H, Lindecrantz K, et al. Fetal ECG waveform analysis should improve fetal surveillance in labour. J. Perinat Med 1990, 18(1): 13-22.

   Observational Study: IRB approval, informed consent

   Cross-Reference Number from Module M001 Bibliography: 45

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
Objective The objective of the study was to evaluate ST waveform changes during labour, using a recording technique with maternal skin as reference. ST waveform changes in the form of T/QRS ratios were correlated to FHR changes, Apgar scores and cord artery acid-base data. Clinical management FHR formed the basis for management of labour. The STAN recorder was used in parallel to a standard CTG recorder. CTG classification FHR recordings were classified as normal, suspicious or abnormal, according to FIGO News 1987 recommendations. ST waveform assessment Baseline and increases for more then 5 minutes in T/QRS ratio were considered. The upper level of normality was set to a T/QRS ratio of 0.25. Negative T wave components were considered abnormal. Respiratory acidaemia Cord artery pH <7.15, standard bicarbonate >15 mmol/l Metabolic acidosis pH <7.15 and standard bicarbonate <15 mmol/l Perinatal asphyxia Cord artery pH <7.15 and standard bicarbonate <15 mmol/l. Apgar score <4 at 1 min and <7 at 5 min.	**ST analyser** STAN 8801 Fetal ECG was obtained from a single spiral electrode with the reference point placed on the maternal thigh. The signal was fed via a preamplifier to a purpose built microprocessor for automatic assessment of the ST waveform. Average T and QRS amplitudes were calculated from 10 ECGs. The resultant quotient was calculated and plotted in analogue form. The ECG signal was sent to a FHR monitor in parallel to STAN.	Patients in labour with gest. age >34 weeks. Patients with antenatal risk factors were preferentially included. 201 fetuses in vertex presentation were included.	**Signal quality** Signal quality was optimal for T/QRS measurements to be made at least every two minutes in 77% of the recordings. In the remaining 23% there were blank periods in the recordings, but since the T/QRS ratio was found be stable, especially during first stage of labour also these recordings were included in the analysis. **Operative interventions** 27 (13%) operative deliveries for fetal distress. 14 with abnormal FHR leading to eight CS and six forceps deliveries. 13 with suspicious FHR leading to six CS and seven forceps deliveries. 11 of the 27 had T/QRS changes with average ratios >0.25. Three of the 27 had cord artery pH <7.15, all of these were identified by elevated T/QRS ratios. **Neonatal outcome** Three babies with clinical evidence for asphyxia. One of these had abnormal FHR trace and was delivered with CS. The other two had suspicious FHR trace. All three cases had T/QRS elevations >0.25. Five babies with metabolic acidosis. All five had T/QRS ratios >0.25 during first stage of labour. There were eight babies with respiratory acidaemia. Five of those had abnormal T/QRS ratios in beginning of last stage, one showed no ST changes (pH=7.14), two showed increased T/QRS ratios 20 min before delivery. In one case a seven-minute bradycardia occurred (FHR <100beats).	The available data showed that: It is possible to use the described STAN system for on-line recording of the unfiltered fetal ECG waveform and to analyze the ST waveform. Acute hypoxia was recognized by a rapid rise in the T/QRS ratio. Changes in the ST interval are related to metabolic events in the myocardium and FHR changes relate to neuro-physiological responses during hypoxia. In other words two different parameters, identifying different responses to fetal hypoxia. The value of combined studies of FHR and ST waveform analysis was illustrated by the data. T/QRS ratio is less sensitive to identify respiratory acidosis. Respiratory acidosis though, is not a major threat to the baby. T/QRS ratio <0.25 identifies with 99.3% accuracy a fetus with normal buffering capacity, independent of FHR tracing. Unnecessary CS could thereby be avoided. Because of the low rate of perinatal asphyxia and because of early interference based on FHR traces, further studies are required to evaluate whether fetal ECG waveform analysis will improve the diagnosis of perinatal asphyxia.

2. Reference: Maclachlan NA, Spencer JAD, Harding K, Arulkumaran S. Fetal acidemia, the cardiotocograph and the T/QRS ratio of the fetal ECG during labor. Br. J. Obstet. Gynaecol. 1992; 99(1): 25-31

Observational Study: IRB approval, informed consent

Cross-Reference Number from Module M001 Bibliography: 114

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
Objective The objective was to compare the sensitivity and the positive predictive value between CTG and elevated T/QRS ratio, with fetal acidaemia during labour and at delivery. FBS pH <7.20 and cord artery pH <7.12 were correlated with T/QRS ratio >0.28 and CTG classification. Clinical management T/QRS data were not used for clinical management. FBS was collected when clinically indicated, usually to assess FHR changes. ST waveform assessment The mean of three T/QRS ratios before FBS (within 10 min.) or delivery (within 30 min.), was taken as representatives for the comparison with pH or neonatal outcome. CTG classification FHR recordings were classified as normal, suspicious or abnormal according to FIGO News 1987 recommendations. Acidaemia Cord artery pH <7.12 Metabolic acidosis Cord artery pH <7.12, BDecf >12.0 mmol/l.	**ST analyser** STAN 8801 FHR was monitored using a Copeland scalp electrode. The same electrode was used for the ECG data to a STAN monitor for on-line calculation and recording of the T/QRS ratio. Maternal skin was used as reference. Average T and QRS amplitudes were calculated from 30 ECGs. The resultant quotient was calculated and plotted in analogue form. **CTG recorders** HP 8031 FM6	113 women in labour with term fetuses (37-42 weeks). Pregnancies with abnormal CTG were preferentially included.	**Signal quality** Interpretable CTG traces within 30 min of labour were available for 93 cases. The quality of ST recordings deteriorated during second stage of labour. CTG versus other factors The group with suspicious and abnormal CTG showed no increase in the rate of operative deliveries or T/QRS ratio >0.28. But they did show a significant lower median cord artery pH (P<0.03 and P<0.001) respectively. Neonatal outcome 17 fetuses were classified as acidaemic and the median T/QRS ratio in this group was significantly higher then in the non acidaemic group (0.21 and 0.13 respectively P<0.001). 13 of the 17 acidaemic babies had a metabolic acidosis. CTG results 13 of the acidaemic babies had abnormal CTG traces. This corresponds to a 38% positive predictive value and 76% sensitivity. ST analysis results The positive predictive value for acidaemia diagnosed solely from elevated T/QRS ratio was 71% and the sensitivity was 29%. T/QRS ratio did not correlate with scalp pH, however in combination with pathologic CTG, scalp pH values of <7.25 showed a strong correlation with increasing T/QRS ratios (r=0.71, P>0.001).	These data confirm that CTG interpretation in clinical practice is inaccurate. Interpretation of CTG changes might be improved if the traces without an associated T/QRS rise could be reliably discounted as false positive. Much larger clinical experiments then are presently available are required before T/QRS ratio could be considered for introduction into clinical practice. The T/QRS ratio should be compared to the neonatal outcome. If it is found to be associated, it could be used to reduce the number of false positives and thereby the intervention rate.

Comments Related to the Paper: The study by Maclachlan et al on 113 term pregnancies used Copeland scalp clip which has been shown to adversely affect not only the quality of the ECG signal but also the presentation of the different frequency components contained within the ECG. Furthermore, no recognition was made of the lag time between the end of the STAN recording and delivery, nor did the work include the assessment of ST waveform configurations, other than elevated T waves. The study showed the limitations of using only T/QRS ratio and focusing on first-stage events, trying to relate these to the outcome of labor. The study did not contain any true case of intrapartum asphyxia, i.e. cord artery pH <7.05 and extracellular fluid base deficit >12 mmol/l. The study illustrated the need for a strict protocol to be followed in the work required to assess the clinical potentials of ST waveform analysis.

3. Reference: Murphy KW, Russell U, Johnson P, Valente J. Clinical assessment of fetal electrocardiogram monitoring in labor. Br J Obstet Gynecol 1992; 99(1): 32-37

Observational Study: IRB approval, informed consent

Cross-Reference Number from Module M001 Bibliography: 56

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
Objective The objective was to investigate the potential of ST waveform analysis during labour. **Clinical management** Observational study. ST waveform assessment Mean T/QRS ratio during one hour, at 4, 8 and 10 cm cervical dilation, was compared with CTG changes and with indices of the infant condition at birth: Apgar scores, cord artery acid-base and need for neonatal care. T/QRS ratio >0.25 was considered outside the normal range. **CTG classification** The CTG was classified as normal according to the Steer criteria (1989). Respiratory acidaemia Cord artery pH <7.12, Metabolic acidosis Cord artery pH <7.12, BDecf >12 mmol/l, Apgar scores <7 at 1 min.	**ST analyser** STAN 8801 prototype FHR was monitored using a standard scalp electrode. The same electrode was used for the ECG data to a STAN monitor for on-line calculation and recording of the T/QRS ratio. Maternal skin was used as reference. Average T and QRS amplitudes were calculated from 30 ECGs. The resultant quotient was calculated and plotted in analogue form.	86 high-risk pregnancies, with a high frequency of inductions, instrumental deliveries, etc.	Signal quality Of the 86 recordings, three were excluded due to poor signal quality. Neonatal outcome Seven infants had respiratory acidaemia. Four had a clinically significant metabolic acidosis. The most severely affected fetus was identified by T/QRS ratio >0.25, early in labour. During the last stage of labour, the T/QRS ratio decreased and biphasic ST segments were identified. One of the fetuses showed T/QRS increase but not >0.25. One was disconnected from ST analysis before the CTG trace started to deteriorate. The last fetus, with only weak signs of metabolic acidosis, was not identified by CTG or ST trace. Correlations No significant relation was found between the one-hour mean T/QRS and Apgar <7 at 1 min or cord artery pH <7.12. There was a statistical significant correlation between one-hour mean T/QRS and BDecf ($r=0.31$, $n=39$, $P<0.05$)	The mean one-hour T/QRS ratio was not a good predictor of low Apgar scores, but it did identify the most severely asphyxiated child. This case also indicates that it might be necessary to also identify other changes in the ST interval, apart from T/QRS ratio. If fetal ECG analysis should have a role in future fetal intrapartum surveillance, it might be in conjunction with CTG. Then ST analysis could be used to decrease unnecessary interventions.

4. Reference: Westgate J, Harris M, Curnow JS, Greene KR. Plymouth randomized trial of cardiotocography only versus ST waveform plus cardiotocogram for intrapartum monitoring in 2400 cases. Am J Obstet Gynecol 1993: 169:1151-60.

   Interventional Study: IRB approval, informed consent

   Cross-Reference Number from Module M001 Bibliography: 95

Objectives/ Protocol	**Methods/materials**	**Patient population**	**Results**	**Comments**
Objective The objective was to investigate if CTG + ST analysis could improve the predictive value of intrapartum surveillance compared to CTG only and thereby decrease interventions, without increased risk for the babies. This prospective clinical trial was divided in a CTG only and a CTG+ST arm. The traces were compared with neonatal outcome and cord acid-base data. Both at delivery and retrospectively. CTG arm Interpretation of CTG and management followed accepted clinical guidelines, including FBS option. In the second stage, acutely emerging ST waveform changes for > 5 min were considered as significant. CTG+ST arm CTG was classified according to the same clinical guidelines as in the CTG arm, but clinical management was modified based on T/QRS ratio and ST segment waveform changes. Metabolic acidosis Cord artery pH <7.05 and BDecf >12mmol/l. **Birth asphyxia** Cord artery pH <7.05, BDecf >12 mmol/l, Apgar scores <7 at 5 min, Active resuscitation for 4 min and problems in the postnatal period.	**ST analyser** STAN 8801 The fetal ECG was recorded using a standard single spiral scalp electrode. Maternal skin was used as reference. The ECG signal was used for on-line calculation and recording of the T/QRS ratio based on 30 beat averaged ECG waveforms. Biphasic/negative ST waveforms were assessed by visual analysis of printed ECG averages. **CTG recorder** HP 8040A **Personnel training** All personnel were trained both in CTG classification and ST analysis before and during the study.	2400 high-risk pregnancies of >34 weeks of gest. with no gross fetal abnormality were included. Entry in either arm was decided by draw of a sealed envelope. CTG arm 1212 cases CTG+ST arm 1188 cases	Signal quality In 12 of the entries ST waveform analysis could not be assessed, due to poor signal quality. Intervention rates There was a 46% reduction ($p<0.001$) in operative deliveries for fetal distress, without an increase in operative deliveries for other reasons. The different CTG patterns were equally distributed in both arms. Neonatal outcome There were more cases of metabolic acidosis (13 vs 5) and more low Apgar scores (<7) (32 vs 20) in the CTG arm. Although this was not statistical significant it showed a trend towards improved short-term neonatal outcome in the ST+CTG arm. There were (4 vs 3) cases of birth asphyxia. Negative ST waveforms There were six cases identified with persistent negative ST waveforms in association with an abnormal CTG trace. All were depressed at birth and required resuscitation. These six included two of the three cases of birth asphyxia in the CTG+ST arm.	The study showed that ST waveform analysis discriminates CTG changes in labour and that the protocol was safe. The results from this study confirm that the ST+CTG analysis significantly reduces interventions without having adverse effects on the neonatal outcome. Further studies are required to statistically verify the trend towards less metabolic acidosis in the CTG+ST arm. The retrospective analysis of data supports the trend in improved neonatal outcome. CTG+ST analysis does not require additional procedures and it provides continuously available information and is therefore more likely to affect appropriate and timely decision making than fetal blood sampling.

Comments Related to the Paper: A retrospective analysis of the CTG showed operative deliveries for fetal distress in 2.7% of cases with normal CTG in the CTG only group, as compared with 0.3% in the STAN group. Cases with an intermediate CTG pattern had operative interventions in 19.5% and 9.6%, respectively, and with an abnormal CTG the intervention rate was 44.4% and 35.3%, respectively. 43% of operative interventions were judged unnecessary in the CTG arm as compared with 5% in the STAN arm of the trial.

There were no significant differences in the measures of neonatal outcome, but fewer low 5 minute Apgar scores and less metabolic acidosis in the ST + CTG arm were apparent, and there was also a significant reduction in the use of fetal blood sampling. 18% of abnormal traces in the CTG arm should have had an intervention (2 cases of asphyxia) as compared with 9% in the STAN arm (1 case of asphyxia).

Three patterns of ST + CTG change occurred:

ST persistently raised, CTG normal

In this group the mean cord artery pH of 7.28 was significantly higher than all the other groupings. We believe the slightly raised ST waveform reflects sympathoadrenal stimulation from the general arousal of labor and the neonatal outcome in these cases was excellent.

ST wave form rising, CTG abnormal and deteriorating

The ST waveform became raised and the CTG abnormal and deteriorated in a group of fetuses with significantly lower mean cord artery pH (7.05; 7.02- 7.08) and higher base deficit (7.6 mmol/l; 6.1-9.1) than all the other groups; still with a normal outcome. We believe this represents fetuses that were developing a metabolic acidosis as a result of significant hypoxia.

ST Segment depressed with biphasic/negative T waves

The ST waveform was negative or the ST segment depressed in a small number, but all of these cases were depressed at birth requiring resuscitation and had low arterial pHs - less than 7.08 and BDecf more than 10 mmol/l (when available). Similar cases have been reported from other groups with metabolic acidosis, growth retardation or asphyxial death. These patterns are therefore entirely consistent with the animal data and do suggest a possibility of distinguishing the normal fetus suffering acute hypoxia, showing ST elevation and high T waves, from the chronically hypoxemic fetus which then suffers further acute hypoxic insult showing negative/biphasic ST waveforms. The 3 fetuses in the CTG+ST arm that was clinically affected, all had ST events that were not recognized by the operator. This finding focused developments on an automatic assessment of ST events and the new STAN S 21 unit was thus designed on the basis of the experience earned during the Plymouth RCT.

Benefits from ST waveform monitoring:

1. The ST waveform provides another physiological variable from the same scalp electrode used to obtain the fetal heart rate.

2. ST waveform change reflects the metabolic events occurring at a tissue level in response to compensatory mechanisms for oxygen lack in a vital central organ. All the evidence from animal data and human studies so far suggest these changes occur before there is any tissue damage.

3. The use of the CTG alone results in much unnecessary and inappropriate intervention. The sensible use of ST waveform in combination with CTG, results in a significant and safe reduction in this intervention.

4. The physiology of ST waveform change is better understood than fetal heart rate change and its use is a good way to introduce clinicians to the complex physiological responses, which occur in labor and thereby improve their interpretation of events as they affect the fetus.

Risks of ST waveform monitoring:

1. High quality signals are needed for ECG analysis and good application of a single spiral fetal scalp electrode is required. Signal noise may give erroneous T/QRS ratio results.

2. Adequate education of staff in the concepts of both ST waveform and CTG analysis is essential for correct clinical interpretation.

3. There is currently too much emphasis on the T/QRS ratio, which has the benefit of being quantifiable but is only one aspect of ST waveform assessment. It is no surprise that studies attempting to correlate T/QRS values with cord artery pH across the normal range of both parameters, hardly find any relationships at all. Important changes in the ST segment such as ST depression may be missed if the whole waveform is not examined. This examination also assesses signal quality and checks that T/QRS measurements are not erroneous as a result of noise.

5. Reference: Luzietti R, Erkkola R, Hasbargen U, Mattsson LA, Thoulon JM, Rosen KG. European Community Multi-Center Trial "Fetal ECG Analysis During Labor": ST plus CTG analysis. J. Perinat. Med. 1999; 27:431-440

   Observational Study: IRB approval, informed consent

   Cross-Reference Number from Module M001 Bibliography: 71

Objectives/ Protocol	Methods/materials	Patient population	Results	Comments
Objective The objective was to identify changes in the fetal ECG waveform in cases of verified fetal hypoxia. In this study, the main focus was on changes in the T/QRS ratio using an automatic system for trend analysis on ST changes together with automatic identification of ECG complexes with ST segment abnormalities, i.e. ST segment depression. Clinical management This was a prospective study and the ECG waveform information was not available to the clinician during delivery. Retrospective assessment The CTG+ST traces were assessed retrospectively and blind to the clinical outcome. The data were grouped according to the CTG+ST clinical guidelines for intervention. Outcome parameters The outcome parameters considered were: birth weight, Apgar scores at 1, 5 and 10 min, cord artery and vein acid-base assessment, need and method of resuscitation and transferral to neonatal intensive care unit. **ST waveform assessment** The ST changes considered were; Episodic T/QRS rise (>0.10 for <10 min.), T/QRS baseline rise (>0.05 for >10 min.) and repeated biphasic STs and appearance of repeated negative T waves with ST depression. ST waveform changes were assessed different depending on the CTG classification	**ST analyser** STAN 8801 recorder connected to a PC for further signal processing, with data reduction and storage. The data was further processed to regenerate a CTG trace and a 30 beat ECG average for ST waveform analysis. The off-line signal checked for signal quality to ensure that only high quality ECG waveforms were included. T/QRS ratio was automatically calculated and ST segments with negative slopes (biphasic ST) were identified. ST waveform changes were identified both through visual inspections of the CTG+ST traces and through an automatic PC based algorithm, the ST Log.	618 cases were recorded, but due to data collection inconsistency only 320 cases could be reviewed and compared with the original case notes. All cases included had a gestational age of >36 weeks.	**Signal quality.** The quality of the traces allowed 84% of the available ECG to be used for FHR analysis and 80% of those for ST analysis. **Neonatal outcome** This data included six cases of intrapartum hypoxia. All were identified by ST events. One additional case had a cerebral bleeding probably associated with a ventouse delivery for failure to progress. **CTG analysis** The CTG was abnormal in 55 cases, at retrospective analysis. **ST waveform analysis** Baseline rise in T/QRS ratio occurred in five cases, all were associated with abnormal CTG. All of these neonates had evidence of intrapartum hypoxia. Episodic T/QRS rise occurred in 16 cases, all except one appeared in association with an abnormal CTG. All babies had an uneventful neonatal period. Biphasic STs were in five cases intermittent, short lasting and associated with a normal CTG. All these cases had a normal outcome. The one baby with persistent biphasic STs and an abnormal CTG, had evidence for intrapartum hypoxia. **Operative deliveries** 30 cases of operative delivery, 18 instrumental vaginal and 12 emergency CS. Operative delivery for fetal distress was performed in only two of the six hypoxic babies.	The strong association between ST waveform changes and adverse intrapartum events is illustrated by the fact that six out of six cases with evidence of intrapartum asphyxia showed ST changes. At the same time four of the most marked asphyxiated cases were not acted upon. Thus, there is little doubt that ST waveform analysis may add to current techniques for intrapartum fetal surveillance. The clinical guidelines used are based on the combined CTG +ST analysis. The latter parameter allows for a most detailed assessment of adverse events in labor associated with hypoxia. A new STAN recorder containing the ST log function is to be tested in a second randomised controlled trial. This study should have power enough to show, to which degree, the perinatal outcome can be improved, using CTG+ST analysis.

6. Reference: ST analysis of the fetal ECG during labor improves the detection of adverse outcome data from a Nordic observational multi-center study. Beta trial (not published data)

   Observational Study: IRB approval, informed consent

   Paper included in Section X of this PMA: Updated Bibliography

Objectives/Protocol	**Methods/materials**	**Patient Population**	**Results**	**Discussion**
Objective As considerable improvements in signal processing occurred after the data collection for the EC multicenter trial was finalised, another retro-spective observational study, to identify changes in the ST waveform was conducted. The accuracy of the STAN clinical guidelines for inter-vention and the new ST log function was also tested. In three of the centres participating, the trial became part of the preparation for the Swedish RCT. Clinical management Observational study, the ST data was available to the clinician but clinical action was based on standard procedures. Retrospective analysis The CTG+ST traces were assessed retrospectively and blind to the clinical outcome. The data were grouped according to the CTG+ST clinical guidelines for intervention. Assessment of the clinical outcome was based on: cord artery and vein acid-base data, Apgar scores, need for resuscitation, referral to neonatal intensive care and signs of neonatal neuromuscular abnormal findings. **ST waveform assessment** The ST changes considered were; Episodic T/QRS rise (>0.10 for <10 min), T/QRS baseline rise (>0.05 for >10 min) and repeated biphasic STs and appearance of repeated negative T waves with ST depression. ST waveform changes were assessed different depending on the CTG classification.	**ST analyser** The prototype of the STAN S 21 (STAN ESST) ST waveform changes were identified both through visual inspections of the CTG+ST traces and through an automatic PC based algorithm called ST log.	574 deliveries with gestational age >36 weeks.	Neonatal outcome 15 cases were identified as being exposed to intrapartum hypoxia. Five of those had neonatal neurological symptoms. All five were identified as abnormal cases according to CTG+ST clinical guidelines during first stage of labour. The other ten babies had metabolic acidosis only (cord artery pH <7.05 and BDecf >12mmol/l). Two had changes in the first stage of labour and the remaining eight showed ST changes during second stage of labour. 12 of the ST events were T/QRS baseline raises. One case displayed an episodic T/QRS increase; one case showed consistent ST depression with negative T waves and the final case had a preterminal CTG as a predominant finding with one episodic T/QRS rise. Eight cases had cord artery acidemia only (pH< 7.05 but BDecf<12 mmol/l). They were all unaffected at birth. Seven of these displayed CTG+ST abnormalities. Clinical guidelines The sensitivity for CTG+ST clinical guidelines to recommend intervention was 100% (15/15) for cases with neonatal symptoms and/or metabolic acidosis and 95.8% (22/23) when the respiratory acidosis cases were included. The corresponding figures for the specificity were 95.0% and 96.4%. Operative interventions The operative intervention rate according to the CTG+ST clinical guidelines was 7.5%, compared to the actual rate of 15.3%	The Plymouth trial showed that cases with ST elevation and abnormal CTG all had cord artery pH 7.15. In the present study, 86% of the cases where the STAN clinical guidelines called for intervention, had cord artery pH 7.15. The difference may be accounted for by the improvements in signal quality and the ability of the ST log to more accurately identify ST changes and biphasic ST patterns at an earlier stage of hypoxia. The experience gained this far demonstrates the ability of CTG+ST clinical guidelines, supported by computerized assessment of ST changes, to identify babies at risk of intrapartum hypoxia. Further progress of the STAN concept will depend on the outcome of the Swedish multicenter randomized controlled trial.